IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF VIRGINIA
Alexandria Division

HALOZYME, INC. Plaintiff, v. JOSEPH MATAL, performing the functions and duties of Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office, Defendant.	Case 1:16-cv-01580-CMH-JFA

HALOZYME'S PRETRIAL PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW*

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* Halozyme, Inc., initially filed this document under seal prior to the commencement of trial (ECF No. 140). Upon further review, Halozyme believes it can be filed publicly. The submission is substantively identical to what was submitted earlier today.

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PROPOSED FINDINGS OF FACT

1. Halozyme, Inc., is a corporation organized under the laws of the State of California with its principal place of business at 11388 Sorrento Valley Road, San Diego, California 92121. [ECF No. 87, 2d Am. Compl. ¶ 3.] Halozyme is the assignee of U.S. Patent Application Serial No. 11/238,171 ("the '171 Application"). [ECF No. 76, Stip. ¶ 1.]

2. Joseph Matal is the Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office. [ECF No. 87, 2d Am. Compl. ¶ 3.]

3. Halozyme brings this action pursuant to 35 U.S.C. § 145 against Mr. Matal—as the head of the PTO—seeking a judgment that Halozyme is entitled to a patent for the invention specified in Claims 295–298, 300, and 303 of the '171 Application ("the Pending Claims"), which claims are the subject of a final decision by the Patent Trial and Appeal Board ("PTAB" or "Board"). [ECF No. 76, Stip. ¶¶ 1, 3, 4.]

4. The Board affirmed the Examiner's obviousness rejection of the Pending Claims under 35 U.S.C. § 103(a) based on three prior art references: (a) Bookbinder et al., WO 2004/078140, published September 16, 2004 ("'140 Bookbinder"), (b) Braxton, U.S. Patent No. 5,766,897, issued June 16, 1998 ("Braxton"), and (c) Thompson et al., U.S. Patent No. 6,552,170, issued April 22, 2003 ("Thompson"). [ECF No. 76, Stip. ¶ 5.]

5. The Board also affirmed the Examiner's rejection on grounds of non-statutory obviousness-type double patenting over U.S. Patent Nos. 7,767,429 (Claims 9 and 10), 7,846,431 (Claims 4 and 5), and 7,829,081 (Claims 5 and 6) in view of Braxton and Thompson. [ECF No. 76, Stip. ¶ 6.]

6. The PTAB Decision on Appeal (Appeal 2014-001770; Application 11/238,171) was mailed on July 27, 2016, and the Request for Rehearing ("RFR Denial") was denied and mailed on October 20, 2016. [PTX37; PTX39.] These decisions constitute a final decision under 37 C.F.R. § 41.2. [ECF No. 76, Stip. ¶ 4.]

7. Halozyme timely commenced this action on December 19, 2016. [ECF No. 76, Stip. ¶ 2.]

8. This Court has jurisdiction and venue pursuant to 35 U.S.C. § 145. [ECF No. 87, 2d Am. Compl. ¶ 5.]

9. U.S. Patent Application Serial No. 11/065,716 ("the '716 Application") was filed on February 23, 2005. [PTX243.] The '171 Application is a continuation-in-part of, and claims priority to, the '716 Application, as the Administrative Record reflects. [PTX26.]

10. The '716 Application provides at least two paragraphs of written description of generating "rHuPH20s reproducibly comprising a combination of molecules having between about three to six PEG molecules per sHASEGP." [PTX243 ¶¶ 815–16.] Paragraph 816 of the '716 Application discloses that these pharmaceutical compositions were intravenously administered (systemic administration) in mice, and showed a 16-20 fold increase in serum half-life over unmodified sHASEGP and further provided therapeutic benefit in a rat stroke model. [PTX243 ¶ 816.]

11. The '716 Application also provides an "illustrative example of the use of pegylation to generate modified forms of sHASEGPs having improved pharmacokinetics, such as increased serum half life, [by] attach[ing] either linear or branched polyethylene glycol (PEG) moieties to an exemplary sHASEGP, recombinant human PH20

(rHuPH20)." [PTX243 ¶ 811.] The '716 Application also teaches that "PEG lengths ranging from 5 to 40 KDa have been conjugated to rHuPH20" and that "succinimidyl PEGs have typically been the most convenient to use in the case of rHuPH20." [PTX243 ¶¶ 813–14.] It further discloses that:

> Using compositions and techniques as described in the art, succinimidyl PEGs have been used to generate rHuPH20s reproducibly comprising a combination of molecules having between about three to six PEG molecules per sHASEGP. Such pegylated rHuPH20 compositions were readily purified to yield compositions having specific activities of approximately 25,000 Unit/mg protein hyaluronidase activity, and being substantially free of non-PEGylated rHuPH20 (less than 5% non-PEGylated). As is known in the art, and described for example in PEGylation references including those cited above, a variety of reagents and techniques are also available for achieving mono-disperse as opposed to poly-disperse PEG products (see, e.g., the reviews and references cited above related to site-specific monoPEGylation and site-directed PEGylation).
>
> Improvements in both pharmacokinetics and pharmacodynamics have been observed in animal models following administration of a PEGylated sHASEGP as compared to the unmodified version of the sHASEGP. For example, following intravenous administration to mice of either 1,000 Units of an unmodified rHuPH20 or 1,000 Units of rHuPH20 conjugated to PEGs having a molecular weight of approximately 40 kDa (rHuPH20-PEG40), it was observed that the serum half-life of neutral active hyaluronidase activity (PH20) in serum of mice treated with rHuPH20-PEG40 was significantly longer (16-20 fold) than that of mice treated with unmodified rHuPH20. In addition, the effectiveness of rHuPH20-PEG40 has been compared to non- PEGylated rHuPH20 in a rat stroke model. Initial results from these studies demonstrate greater effectiveness of rHuPH20-PEG40 (greater than 75% survival, versus less than 50% in controls) in rat survival 7 days post stroke-inducement.

[PTX243 ¶¶ 815–16.]

12. The '716 Application also explains that "substantially purified polypeptides that include a Hyaluronidase domain of a sHASEGP polypeptide or a catalytically active portion thereof, but that do not include the entire sequence of amino acids set forth in SEQ ID No. 1 are provided. Among these are polypeptides that include a sequence of amino acids that has at least 70%, 80%, 85%, 90%, 95% or 100% sequence identity to SEQ ID No. 1 or 3." [PTX243 ¶ 39.] The specification further describes

sHASEGPs to include the specific glycosylation and amino acid SEQ IDs as claimed. [PTX243 ¶¶ 117, 129.] Because the full-length hyaluronidase is not very soluble due to a membrane-binding domain, truncated versions are taught to create a soluble human PH-20 hyaluronidase glycoprotein. [PTX243 ¶¶ 692–706; *see also id.* ¶ 704 (table of truncated versions including 1-347; 1-372, 1-394; 1-413; 1-430; 1-447; 1-467; 1-477; 1-478; 1-479; 1-480; 1-481; 1-482; 1-483).]

13. Finally, the ’716 and ’171 Application specifications disclose identical full-length and truncated amino acid sequences of the claimed human recombinant hyaluronidase. [PTX243 at 279–308.] For example, SEQ ID No. 4 corresponds to amino acids 36-483 of SEQ ID No. 1. [PTX243 at 279, 282–283.] As Dr. Zalipsky testified, the ’716 disclosure covers all these sequences, and probably a wider variety of sequences. [Zalipsky Test.]

14. Written description and enablement support exists in the ’716 Application for the Pending Claims on a claim-by-claim, limitation-by limitation basis. [Zalipsky Test.]

15. On October 16, 2007, during the prosecution of the ’171 Application, the PTO issued a restriction requirement. [PTX23.]

16. In response, and after electing the Pending Claims to be pursued for prosecution, Petitions to Correct Inventorship were filed on April 16, 2008 and on October 7, 2010. [PTX24; PTX25.] Those petitions identified Louis Bookbinder, Anirban Kundu, and Gregory Frost as the joint inventors on the ’171 Application. [PTX24; PTX25.]

17. The PTO formally corrected inventorship on the ’171 Application identifying Louis Bookbinder, Anirban Kundu, and Gregory Frost as the joint inventors. [PTX26.]

18. WO 2004/078140 (Bookbinder) published on September 16, 2004, and lists Louis Bookbinder, Anirban Kundu, and Gregory Frost as the joint inventors. [PTX29.] Therefore, Bookbinder published less than one year prior to the ’171 Application's claimed priority date of the ’716 Application, which was filed on February 23, 2005. (*See supra* para. 9.)

19. The inventors on Bookbinder and the ’171 Application are the same. (*See supra* paras. 17–18.)

20. The general state of the art on PEGylating for achieving the balance of sufficient enzymatic activity and prolonged circulation for enzymes that act on macromolecular substrates (such as hyaluronidase) was, and continues to remain very challenging with a low expectation of success, particularly by nonspecific amine-directed PEGylation. [Zalipsky Test.]

21. The PTAB’s decision says nothing more than what was generalized in the art, namely attach one or more PEGs to a protein without abolishing its activity. [Flamion Test.] At best, this is a general plan or hypothesis and it does not teach one of skill the general or specific conditions required for any particular number of PEGs (much less where) to attach to the claimed composition which has approximately 447 amino acids without abolishing its in vivo activity, much less on a glycosylated protein where the glycans are essential for activity in a manner that does not interfere with the in vivo activity at the distal tissues. [Flamion Test.] The claimed human-derived hyaluronidase

has 30 lysines and an N-terminal amino group that result in a large number of potential PEGylation sites. [Flamion Test.] Moreover, neither Thompson nor Braxton provide the solution or the general or specific conditions applicable to this unique protein in order to achieve the invention claimed. [Flamion Test.]

22. Human-derived hyaluronidase is a virtually unique glycoprotein that presents specific issues on whether one of skill would be motivated to PEGylate it with three to six PEG moieties to be used in a systemic administration where activity must be achieved at distal tissues, much less have a reasonable expectation of success. [Flamion Test.; Zalipsky Test.]

23. It was no simple matter to successfully make this human derived hyaluronidase with about three to six PEG moieties for use in a systemic application that would have suitable activity and half-life in the body to reach the distal tissues, as the inventor also testified. [Frost Dep. 40:1–46:20, 100:17–106:6, 107:15–117:8.]

24. Claim 264 of the ’171 Application recites: “A pharmaceutical composition, comprising a PEGylated hyaluronidase in a pharmaceutically acceptable carrier, wherein: the hyaluronidase contains about three to six PEG moieties per hyaluronidase molecule; the hyaluronidase polypeptide is a human-derived hyaluronidase; and the composition is formulated for systemic administration.” [ECF No. 76, Stip. ¶ 7(a).]

25. Claim 264 requires a pharmaceutical composition containing a specifically “formulated” human derived hyaluronidase of three to six PEGs for systemic administration. Properly construed as read by one of ordinary skill, those limitations in combination convey to one of ordinary skill in the art that there must be a suitable serum

half-life and activity for the pharmaceutical composition to be used for systemic administration. [Zalipsky Test.; Flamion Test.]

26. Claim 295 of the ’171 Application recites: “The pharmaceutical composition of claim 264 that comprises a Pegylated hyaluronidase that is active at neutral pH and contains at least one sugar moiety that is covalently attached to an asparagine (N) residue of the hyaluronidase polypeptide, wherein: the hyaluronidase polypeptide is a C-terminal truncated polypeptide of SEQ ID NO:1; and contains amino acid residues 36-464 as set forth in SEQ ID NO:1 but does not include the complete sequence of amino acids set forth in SEQ ID NO:1 or contains a sequence of amino acid residues that has at least 95% amino acid sequence identity with the sequence of amino acids 36-464 set forth in SEQ ID NO:1.” [ECF No. 76, Stip. ¶ 7(b).]

27. Claim 296 of the ’171 Application recites: “The pharmaceutical composition of claim 264, wherein: the Pegylated hyaluronidase is active at neutral pH and contains at least one sugar moiety that is covalently attached to an asparagine (N) residue of the hyaluronidase polypeptide; and a) the hyaluronidase consists of the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1; or b) the hyaluronidase contains amino acid substitutions in the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1, whereby the amino acid-substituted hyaluronidase glycoprotein consists of a sequence of amino acids that has at least 95% amino acid sequence identity with the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1.” [ECF No. 76, Stip. ¶ 7(c).]

28. Claim 297 of the ’171 Application recites: “The pharmaceutical composition of claim 296, wherein a hyaluronidase in the composition consists of amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1.” [ECF No. 76, Stip. ¶ 7(d).]

29. Claim 298 of the ’171 Application recites: “The pharmaceutical composition of claim 295, wherein the hyaluronidase glycoprotein is produced by expression of a nucleic acid molecule that encodes amino acids 1-482 or 36-482 of SEQ ID NO:1 in a mammalian cell.” [ECF No. 76, Stip. ¶ 7(e).]

30. Claim 300 of the ’171 Application recites: “The pharmaceutical composition of claim 264, wherein the hyaluronidase polypeptide has a sequence of amino acids that has [at] least 95% sequence identity to the sequence set forth in SEQ ID NO:4.” [ECF No. 76, Stip. ¶ 7(f).]

31. Claim 303 of the ’171 Application recites: “The pharmaceutical composition of claim 264, wherein the hyaluronidase polypeptide consists of a sequence of amino acids that has at least 98% amino acid sequence identity with the sequence of amino acids set forth as residues 36-483 in SEQ ID NO:1.” [ECF No. 76, Stip. ¶ 7(g).]

32. The ’171 Application’s specification teaches that the specifically formulated human hyaluronidase with about three to six PEG moieties, as a pharmaceutical composition for use in systemic administration, has a serum “half-life” and “activity,” as disclosed in the specification’s example 21A. [Zalipsky Test.]

33. The teachings of the specification as read by one of ordinary skill in the art are that one of skill would understand that the Claim 264’s limitations of “pharmaceutical composition” and formulated for “systemic administration,” along with the intended

utility, all illustrate that level of serum half-life and therapeutic effect at the distal tissues are limitations of the inventions claimed. [Flamion Test.; Zalipsky Test.]

34. Claim 10 of the ’429 patent depends on claim 9, which in turn depends on claim 7. [ECF No. 76, Stip. ¶ 9.]

35. Claim 7 of the ’429 patent recites: “A substantially purified hyaluronidase glycoprotein, wherein the hyaluronidase glycoprotein: is soluble; is neutral active; contains at least one sugar moiety that is covalently attached to an asparagine (N) residue of the polypeptide; and consists of the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 set forth in SEQ ID NO:1 or contains amino acid substitutions in the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1, whereby the amino-acid substituted hyaluronidase glycoprotein consists of a sequence of amino acids that has at least 95% amino acid sequence identity with the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1.” [ECF No. 76, Stip. ¶ 10.]

36. Claim 9 of the ’429 patent recites: “The hyaluronidase glycoprotein of claim 7, wherein the hyaluronidase glycoprotein is modified with a polymer.” [ECF No. 76, Stip. ¶ 11.]

37. Claim 10 of the ’429 patent recites: “The hyaluronidase glycoprotein of claim 9, wherein the polymer is PEG or dextran.” [ECF No. 76, Stip. ¶ 12.]

38. Claim 5 of the ’431 patent depends on claim 4, which in turn depends on claim 1. [ECF No. 76, Stip. ¶ 14.]

39. Claim 1 of the ’431 patent recites: “A pharmaceutical composition, comprising: a) a hyaluronidase glycoprotein that is active at neutral pH and contains at least one sugar moiety that is covalently attached to an asparagine (N) residue of the hyaluronidase polypeptide, wherein: (i) the hyaluronidase glycoprotein consists of the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1; or (ii) the hyaluronidase glycoprotein contains amino acid substitutions in the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1, whereby the amino acid-substituted hyaluronidase glycoprotein consists of a sequence of amino acids that has at least 95% amino acid sequence identity with the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1; and b) an insulin that comprises an insulin selected from among an insulin lispro, an insulin glargines, an NPH insulin and a recombinant insulin.” [ECF No. 76, Stip. ¶ 15.]

40. Claim 4 of the ’431 patent recites: “A pharmaceutical composition of claim 1, wherein the hyaluronidase glycoprotein is modified with a polymer.” [ECF No. 76, Stip. ¶ 16.]

41. Claim 5 of the ’431 patent recites: “A pharmaceutical composition of claim 4, wherein the polymer is PEG or dextran.” [ECF No. 76, Stip. ¶ 17.]

42. Claim 6 of the ’081 patent depends on claim 5, which in turn depends on claim 1. [ECF No. 76, Stip. ¶ 19.]

43. Claim 1 of the ’081 patent recites: “A pharmaceutical composition, comprising: a) a hyaluronidase glycoprotein that is active at neutral pH and contains at

least one sugar moiety that is covalently attached to an asparagine (N) residue of the hyaluronidase polypeptide, wherein: (i) the hyaluronidase glycoprotein consists of the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1; or (ii) the hyaluronidase glycoprotein contains amino acid substitutions in the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1, whereby the amino acid-substituted hyaluronidase glycoprotein consists of a sequence of amino acids that has at least 95% amino acid sequence identity with the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1; and b) a cosmetic agent." [ECF No. 76, Stip. ¶ 20.]

44. Claim 5 of the '081 patent recites: "A pharmaceutical composition of claim 1, wherein the hyaluronidase glycoprotein is modified with a polymer." [ECF No. 76, Stip. ¶ 21.]

45. Claim 6 of the '081 patent recites: "A pharmaceutical composition of claim 5, wherein the polymer is PEG or dextran." [ECF No. 76, Stip. ¶ 22.]

46. The Pending Claims are patently distinct from Claim 6 of the '081 Patent. [Flamion Test.]

47. Braxton teaches that proteins PEGylated using site specific conjugation to cysteine residues (the invention claimed therein) have certain properties that are tied to cysteine conjugation on the protein:

> The invention relates to identifying cysteine residues, or amino acid residues which may be substituted by cysteine, and attaching polyethylene glycol to the this group of cysteine, thereby increasing protein stability without abolishing biological activity.

[PTX30 1:20–25; *see also* PTX30 10:26–52; Zalipsky Test; Flamion Test.]

48. Braxton states that the then-standard lysine approach "suffers from the problems associated with partial, random modification of protein and the potential for losing activity if lysine residues are essential for biological activity." [PTX30 2:62-65.]

49. Braxton discourages the random, multi-PEGylation of the lysine residues that Halozyme employs Halozyme in PEGylating its human-derived hyaluronidase of the claimed invention by teaching that PEGylating lysine residues is random and "result[s] in the production of a heterogeneous mixture of PEGylated proteins which differ in both the number and position of PEG groups attached" rendering "[s]uch mixtures of diversely modified proteins [] not suitable as pharmaceutical compositions." [PTX30 2:23–34.] The express claim language in the '171 Application is directed to "a pharmaceutical composition," confirming how one of skill would understand Braxton to teach away from the claimed inventions because lysine conjugation is "not suitable" for pharmaceutical compositions. Braxton also notes that while there are several other methods for protein modification with PEG through free lysine residues, "each suffers from the problems associated with partial, random modification of protein and the potential for losing activity if lysine residues are essential for biological activity." [PTX30 2:60–65; Zalipsky Test.; Flamion Test.]

50. Braxton goes on to suggest that the "ratio of PEG to protein is preferably 1:1, more preferably 2:1, even more preferably 5:1, up to 10:1 or 40:1 ratio of PEG molecules to protein." [PTX30 13:4–7.] Braxton also teaches that the "actual number of PEG molecules covalently bound per chemically modified protein of the invention may vary widely depending upon the desired protein stability (e.g., serum half-life) and the protein used for chemical modification." [PTX 30 12:55–59.] Further, the chemically

modified proteins of the Braxton invention relate specifically to cysteine- PEGylated proteins. Braxton also states that "[p]referably the chemically modified protein composition produced by the subject invention will be homogenous with respect to the position of the cysteine residue(s) modified and the number of cysteine residue(s) modified." [PTX30 13:7–10.] The goal of utilizing site-specificity is to attach one or at best, two PEGs, at sites where they are beneficial and do not adversely affect properties of the conjugate. [Zalipsky Test.; PTX232; PTX235; PTX237.] Thus, the higher ratios of PEG, i.e., introduction of multiple cysteines to a protein for the purpose of PEGylation, is counterproductive with the intent and goals of Braxton, because as multiple cysteines are introduced, it is likely to lead to heterogeneous, improperly folded, and inactive protein aggregates. [Zalipsky Test.; PTX232; PTX235; PTX237.]

51. Thompson, like Braxton, highlights the problems associated with non-specific PEGylation at lysine residues:

> PEGylation of proteins illustrates some of the problems that have been encountered in attaching PEG to surfaces and molecules. The vast majority of PEGylating reagents react with free primary amino groups of the polypeptide. Most of these free amines are the epsilon amino group of lysine amino acid residues. Typical proteins possess a large number of lysines. Consequently, random attachment of multiple PEG molecules often occurs leading to loss of protein activity.
>
> In addition, if the PEGylated protein is intended for therapeutic use, the multiple species mixture that results from the use of non-specific PEGylation leads to difficulties in the preparation of a product with reproducible and characterizable properties. This non-specific PEGylation makes it difficult to evaluate therapeutics and to establish efficacy and dosing information. The site selective PEGylation of such proteins could lead to reproducibly-modified materials that gain the desirable attributes of PEGylation without the loss of activity.

[PTX31 2:10–28.] Thompson teaches site-specific, mono-PEGylation at the cysteine residues. [*See* PTX31 3:42–55, 6:42–43, 7:12–15, 7:15–17; Zalipsky Test.; Flamion Test.]

52. Thompson teaches making a "dumbbell" conjugate with a bivalent PEG in-between two proteins as illustrated by the Abstract which states that "[c]ompounds are disclosed having the general formula R1-X-R2, wherein R1 and R2 are biologically active groups, at least one of which is a polypeptide." [PTX31.] PEG serves as a spacer in these constructs, not a properties modifier. [Zalipsky Test.]

53. One of ordinary skill would understand that Braxton and Thompson teach PEG conjugations to cysteine amino acids that if done with human-derived hyaluronidase, would likely destroy the requisite activity of the human-derived hyaluronidase, rendering it inoperable. [Zalipsky Test.; Flamion Test.; PTX72; PTX106; PTX113; PTX116; PTX124; PTX101; PTX110.]

54. Braxton and Thompson's preference for mono-PEGylation at the cysteine residues teaches away from the about three to six PEG moieties as required in Claim 264. [Zalipsky Test.]

55. Both Braxton and Thompson teach away from using the random, multi-PEGylation of lysine residues stating that such approach often leads to loss of activity and high composition heterogeneity making the conjugates unsuitable for pharmaceutical compositions. [Zalipsky Test.]

56. One of ordinary skill would not know whether 3-6 PEGs would retain sufficient activity and circulatory serum half-life to make it suitable for use as a pharmaceutical composition formulated for systemic administration as claimed in the '171 Application because the claimed human-derived hyaluronidase contains many residues that could potentially be PEGylated, and there are many additional variables that may lead to an uncertain outcome. [Zalipsky Test.]

57. Site-specific PEGylation, not lysine PEGylation, would have been a more favored approach for the claimed invention of the ’171 Application. [Zalipsky Test.]

58. Halozyme has raised $135 million from investors because of PEGPH20. [LaBarre Test.; PTX222; PTX219; PTX223.] These investors chose to financially support Halozyme as opposed to other investment opportunities. [Saxe Test.][1]

59. The company’s presolicitation filings with the SEC state that the purpose of the funds sought is to develop the PEGPH20 product. [PTX219.]

60. The first reason given to investors by the company to invest in it—and the one to which most of the presentation’s space is devoted—is the PEGPH20 product. [PTX223 at 2, 3, 4–15, 20.]

61. Halozyme has agreements with a nationally recognized cancer center, a public university, and a hospital system regarding clinical study of the PEGPH20 product and has been approached by at least two other universities. [LaBarre Test.] Most of these research partners sought Halozyme out and not the other way around. [PTX127; PTX128; PTX129; PTX130; PTX133.] In addition, Halozyme has an agreement with a large pharmaceutical company in which each company will study the other’s product. [PTX131.] Finally, Halozyme has an agreement with a national organization focused on pancreatic cancer that will facilitate the clinical study of the PEGPH20 product. [PTX132.] In each of these instances, Halozyme’s partner commits resources that it could commit elsewhere) to further the development of PEGPH20. [Saxe Test.]

[1] Halozyme assumes that Ivan Hofmann will testify, in which case Jon Saxe will testify in rebuttal.

62. The PEGPH20 product incorporates the Pending Claims. [Flamion Test.; Zalipsky Test.]

63. One of ordinary skill armed with the knowledge that the half-life of human hyaluronidase is extremely short and PEGylation generally causes a decrease in protein activity would not have expected useful therapeutic results as required by the Pending Claims from modifying rHuPH20 with PEGylation, much less with 3-6 PEG moieties. [Flamion Test.; Zalipsky Test.] The claimed PEGylated rHuPH20 of the '171 Application overcomes problems associated with systemic administration of native rHuPH20 as claimed in '140 Bookbinder, namely short half-life and insufficient enzymatic activity. [Flamion Test.; Zalipsky Test.] Importantly, it is the addition of 3-6 PEG moieties that retains the necessary properties (i.e., increase half-life while retaining sufficient enzymatic activity) to make it useful as a therapeutic or pharmaceutical composition for systemic (intravenous) administration as claimed in the '171 Application. [Flamion Test.; Zalipsky Test.]

64. The molecular weight of each individual PEG moiety and the total molecular weight of the end product conjugate have a great impact on the activity of enzymes with large macromolecular substrates. [Zalipsky Test.] For such enzymes, smaller molecular weight PEGs are generally preferred to preserve enzyme activity. [Zalipsky Test.] Additionally, mono-PEGylation is particularly preferred via site-specific modification to minimize activity impairment. rHuPH20 is already a large enzyme in its native form that catalyzes a macromolecular substrate, hyaluronan. [Zalipsky Test.] One of ordinary skill would expect that in such case, smaller molecular weight PEG moieties and fewer PEGs, with a preference to mono-PEGylation would be required to balance the

need to increase half-life while retaining sufficient enzymatic activity for use as a therapeutic. [Zalipsky Test.] The inventors' data showing that the attachment of up to 3-5 PEG moieties, each of molecular weight 30 kDa, was required to achieve maximum increase in half-life while still retaining substantial enzymatic activity is a surprising and unexpected result. [PTX32 at 6–7; *see also* PTX21 ex. 21-A.] This is an unusually high number to retain such enzymatic activity considering the large molecular weight of the enzyme and substrate. [Zalipsky Test.] None of the cited references, singly or in combination, teach or suggest that 3-6 PEG moieties as claimed in the PEGylated rHuPH20 of the '171 Application is important and necessary to achieve the balance of significantly increasing half-life while retaining sufficient enzymatic activity for use as a therapeutic. [Zalipsky Test.]

65. The differences in the prior art were complex and the challenges faced by the Halozyme inventors stemmed from a multitude of different available approaches and unpredictable results of attempting to apply such approaches to meet such needs. [Flamion Test.] PEGPH20 meets a long-felt medical need that is not met by currently available medications. [Flamion Test.] Currently, it is the only product of its kind, comprising a unique therapeutic in comparison to existing therapies in that PEGPH20 has been shown to achieve significant improvements in intratumoral perfusion and drug delivery through targeting of co-administered cancer therapies, especially for pancreatic cancer (as discussed further below), which is one of the deadliest cancers around. [Flamion Test.] PEGPH20 has little toxicity of its own since it does not attack the DNA or other essential molecular machinery within cells, as chemotherapeutic agents do.

[Flamion Test.] This allows PEGPH20 to be combined with these chemotherapies without increasing their toxicities in a significant way. [Flamion Test.]

66. The mechanism of action of Halozyme's PEGPH20 in various types of cancer is to target and deplete hyaluronan in the tumor microenvironment and thereby increase access for therapeutics. [PTX123.] Halozyme has focused on "[t]umors with High Unmet Need" including first-line metastatic pancreatic cancer and advanced non-small cell lung, second-line metastatic gastric, and second-line stage IV breast cancers. [PTX123 at 18.] One example is pancreatic ductal adenocarcinoma (PDAC). PDAC has "claimed notoriety by proving to be one of the most recalcitrant solid-organ malignancies. As a telltale sign of its lethality, PDAC accounts for less than 3% of new cancers diagnosed annually in developed nations and in the United States, yet it is the fourth leading cause of cancer related mortality. Ominously, PDAC is also poised to surpass breast, prostate and colon cancers to become the second leading cancer related cause of death by 2030." [PTX122 at 367.] Notably, most patients with PDAC are not candidates for surgical resection owing to the late stage at presentation, and even those patients with early-stage disease who undergo surgical resection and adjuvant therapy eventually relapse and succumb to it. [PTX122 at 367.] In exploring recent advances in molecularly targeted therapies in PDAC, Narayanan and Weekes stated that "PEGPH20 [co-administered with] gemcitabine resulted in an 83% increase in survival and a dramatic decrease in metastatic burden in mice, owing to the enhanced delivery of gemcitabine to the tumor." [PTX122 at 370.] The authors go on to note that initial phase II trial reports "demonstrate that patients with high hyaluronan expressing tumors have greater clinical benefit." [PTX122 at 370.]

67. PEGPH20 is not yet approved by the FDA, but is currently undergoing clinical trials with positive and promising results. [*See, e.g.*, PTX121.]

68. Halozyme and a major pharmaceutical company entered into a Combination Study Agreement in November 2016 to use PEGPH20 in combination with cisplatin and gemcitabine and/or atezolizaumab in subjects with previously untreatable gallbladder cancers in a clinical study. [PTX131.] In another example, a national organization focused on pancreatic cancer entered into an agreement with Halozyme in December 2016 to use Halozyme's PEGPH20 in subjects diagnosed with pancreatic cancer. [PTX132.]

69. Halozyme also receives numerous applications from third parties for investigator sponsored trials. [*See, e.g.*, PTX128 (hypothesizing that adding PEGPH20 to standard of care MM-398 + 5-FU/LV will result in overall survival improvements in subjects with pancreatic ductal adenocarcinoma (PDAC)); PTX129 (PEGPH20 in combination with Folfirinox for patients with locally advanced pancreatic cancer, a disease with a five year overall survival rate of less than 7%).] These types of applications have resulted in a number of Investigator-Initiated Clinical Research Study Agreements between Halozyme and third party entities. [PTX127 (protocol notes PDAC is the 4th leading cause of cancer mortality in the U.S. and chemotherapy have only proven to be modestly effective as a treatment, whereas in a mouse model of PDAC, PEGPH20 was shown to rapidly and sustainably deplete hyaluronan and increase intratumoral delivery of two chemotherapeutic agents); PTX130 (protocol hypothesizing that preoperative treatment with PEGPH20 will increase intratumoral perfusion and drug delivery without increased risk of post-operative complication); PTX133 (protocol stating

that PEGPH20 "uses a novel mechanism of action to systemically target tumors that accumulate the substrate for this enzyme, hyaluronan (HA)").] These clinical collaborations and Investigator-Initiated Clinical Research Study Agreements are a direct result of the industry's recognition of and desire for the claimed invention of the '171 Application. [Flamion Test.]

PROPOSED CONCLUSIONS OF LAW

A plaintiff in a civil action under 35 U.S.C. § 145 is "free to introduce new evidence in Section 145 proceedings subject only to the rules applicable to all civil actions, the Federal Rules of Evidence and the Federal Rules of Civil Procedure." *Kappos v. Hyatt*, 132 S. Ct. 1690, 1700 (2012) (rejecting PTO argument that challenged administrative record is entitled to deference).[2] Where, as here, "new evidence is presented on a disputed question of fact, the district court must make de novo factual findings that take account of both the new evidence and the administrative record before the PTO. *Id.* at 1701; *see also id.* at 1696 (rejecting "deferential standard of review" of PTAB decision in Section 145 action); *see also BTG Int'l Ltd. v. Kappos*, No. 1:12-CV-682, 2012 WL 6082910, at *4 (E.D. Va. Dec. 6, 2012). Halozyme may raise new issues not raised or considered by the USPTO or by the PTAB. *Disney Enters., Inc. v. Kappos*, 923 F. Supp. 2d 788, 802 (E.D. Va. 2013).

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[2] 35 U.S.C. § 145 provides:

> [a]n applicant dissatisfied with the decision of the Patent Trial and Appeal Board in an appeal under section 134(a), may . . . have remedy by civil action against the Director in the United States District Court for the Eastern District of Virginia . . . . The court may adjudge that such applicant is entitled to receive a patent for his invention, as specified in any of his claims involved in the decision of the [USPTO], as the facts in the case may appear and such adjudication shall authorize the Director to issue such patent on compliance with the requirements of law.

35 U.S.C. § 145.

The judicially created doctrine of obviousness-type double patenting—on which the PTAB relied—is intended to "prevent the extension of the term of a patent . . . by prohibiting the issuance of the claims in a second patent not patentably distinct from the claims of the first patent." *Eli Lilly & Co. v. Teva Parenteral Meds, Inc.*, 689 F.3d 1368, 1376 (Fed. Cir. 2012). The obviousness-type double patenting inquiry consists of two steps: "First, the court construes the claim[s] in the earlier patent and the claim[s] in the later patent and determines the differences. Second, the court determines whether those differences render the claims patentably distinct." *AbbVie Inc. v. Mathilda & Terence Kennedy Inst. Rheumatology Trust*, 764 F.3d 1366, 1373 (Fed. Cir. 2014).

The second step "of the obviousness-type double patenting analysis is analogous to an obviousness analysis under 35 U.S.C. § 103." *Id.* at 1378. While the ultimate question of obviousness under 35 U.S.C. § 103 is a matter of law, this determination rests on several factual inquires, including: "(1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the art; and (4) objective considerations of nonobviousness." *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). The obviousness inquiry is made from the perspective of a person of ordinary skill in the art at the time of the invention. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007).

In assessing the patentable distinction, "the claims must be considered as a whole," i.e., the district court should "examin[e] whether one of ordinary skill in the art would have been motivated to modify the [reference] Compound to create [the compound of the asserted claim], considering the compounds as a whole." *Eli Lilly*, 689 F.3d at 1377. "Patentability shall not be negated by the manner in which the invention was made." 35 U.S.C. § 103(a).

I. The Pending Claims Are Not Obvious Under 35 U.S.C. § 103 over Bookbinder in View of Braxton and Thompson.

One's own invention, whatever form of disclosure to the public, may not be prior art against oneself, absent a statutory time bar. 35 U.S.C. § 102(a), (e); *In re Katz*, 687 F.2d 450, 454 (Fed. Cir. 1982). Accordingly, if the Pending Claims are entitled to the priority date of February 23, 2005, Bookbinder may be prior art only if it is by "another." Here, priority of the Pending Claims to the February 23, 2005 '716 Application is established because Halozyme affirmatively showed written description and enablement support for the Pending Claims. The three named inventors are the same on Bookbinder patent application as the '171 Application, i.e., Louis Bookbinder, Anirban Kundu, and Gregory Frost. The Bookbinder patent application is not by "another" and therefore is not prior art to the Pending Claims.

A. The '716 Application Provides Sufficient Written-Description Support for the Pending Claims.

When a party seeks the benefit of an earlier-filed United States patent application, the earlier application must meet the requirements of 35 U.S.C. § 120 and 35 U.S.C. § 112 ¶ 1, which means the earlier application must contain a written description of the subject matter and must meet the enablement requirement. *See Hyatt v. Boone*, 146 F.3d 1348, 1352 (Fed. Cir. 1998). 35 U.S.C. § 120 allows a later-filed patent application to claim the benefit of an earlier filing date in the United States if "the claims of the later-filed application [are] supported by the written description in the parent 'in sufficient detail that one skilled in the art can clearly conclude that the inventor invented the claimed invention as of the filing date sought.'" *EnOcean GmbH v. Face Intern. Corp.*, 742 F.3d 955, 960 (Fed. Cir. 2014). In this case, the '716 Application contains sufficient written-description support for the Pending Claims.

Speaking from the perspective of one skilled in the art, Dr. Zalipsky provided evidentiary support on a claim-by-claim, limitation-by limitation basis in opining that the '716 Application

adequately describes and enables the Pending Claims of the '171 Application. (PFoF ¶ 14); *see Ariad Pharms, Inc. v. Eli Lilly and Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (the written description "test requires an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art."). For example, the '716 Application provides an "illustrative example of the use of pegylation to generate modified forms of sHASEGPs having improved pharmacokinetics, such as increased serum half life, [by] attach[ing] either linear or branched polyethylene glycol (PEG) moieties to an exemplary sHASEGP, recombinant human PH20 (rHuPH20)." (PFoF ¶ 11.) The '716 Application also teaches that "PEG lengths ranging from 5 to 40 KDa have been conjugated to rHuPH20" and that "succinimidyl PEGs have typically been the most convenient to use in the case of rHuPH20." (PFoF ¶ 11.) It further discloses that:

> Using compositions and techniques as described in the art, succinimidyl PEGs have been used to generate rHuPH20s reproducibly comprising a combination of molecules having between about three to six PEG molecules per sHASEGP. Such pegylated rHuPH20 compositions were readily purified to yield compositions having specific activities of approximately 25,000 Unit/mg protein hyaluronidase activity, and being substantially free of non-PEGylated rHuPH20 (less than 5% non-PEGylated). As is known in the art, and described for example in PEGylation references including those cited above, a variety of reagents and techniques are also available for achieving mono-disperse as opposed to poly-disperse PEG products (see, e.g., the reviews and references cited above related to site-specific monoPEGylation and site-directed PEGylation).
>
> Improvements in both pharmacokinetics and pharmacodynamics have been observed in animal models following administration of a PEGylated sHASEGP as compared to the unmodified version of the sHASEGP. For example, following intravenous administration to mice of either 1,000 Units of an unmodified rHuPH20 or 1,000 Units of rHuPH20 conjugated to PEGs having a molecular weight of approximately 40 kDa (rHuPH20-PEG40), it was observed that the serum half-life of neutral active hyaluronidase activity (PH20) in serum of mice treated with rHuPH20-PEG40 was significantly longer (16-20 fold) than that of mice treated with unmodified rHuPH20. In addition, the effectiveness of rHuPH20-PEG40 has been compared to non- PEGylated rHuPH20 in a rat stroke model. Initial results from these studies demonstrate greater effectiveness of rHuPH20-PEG40 (greater than 75% survival, versus less than 50% in controls) in rat survival 7 days post stroke-inducement.

(PFoF ¶ 11.)

Moreover, the full-length polypeptide sequence of the claimed human recombinant hyaluronidase disclosed in the ’716 Application encompasses the sequences of amino acids claimed in the ’171 Application. The ’716 Application also explains that “substantially purified polypeptides that include a Hyaluronidase domain of a sHASEGP polypeptide or a catalytically active portion thereof, but that do not include the entire sequence of amino acids set forth in SEQ ID No. 1 are provided. Among these are polypeptides that include a sequence of amino acids that has at least 70%, 80%, 85%, 90%, 95% or 100% sequence identity to SEQ ID No. 1 or 3.” (PFoF ¶ 12.) The specification further describes sHASEGPs to include the specific glycosylation and amino acid SEQ IDs as claimed. (PFoF ¶ 12.) Because the full-length hyaluronidase is not very soluble due to a membrane-binding domain, truncated versions are taught to create a soluble human PH-20 hyaluronidase glycoprotein. (PFoF ¶ 12.)

Finally, the ’716 and ’171 Application specifications disclose identical full-length and truncated amino acid sequences of the claimed human recombinant hyaluronidase. (PFoF ¶ 13.) For example, SEQ ID No. 4 corresponds to amino acids 36-483 of SEQ ID No. 1. (PFoF ¶ 13.) As Dr. Zalipsky testified, the ’716 disclosure covers all these sequences, and probably a wider variety of sequences. (PFoF ¶ 13.) The written description requirement does not demand that the “specification recite the claimed invention in haec verba.” *Ariad*, 598 F.3d at 1352. Indeed, the Federal Circuit has rejected any characterization of the written description doctrine as a “super enablement” standard for chemical and biotechnology inventions. *Id.*

The claims at issue here are directed to a pharmaceutical composition that is formulated for systemic administration that comprises a neutral active human derived hyaluronidase with

about three to six PEG moieties with specific amino acid sequences—all of which are disclosed in the ’716 Application.

B. Bookbinder and the Pending Claims Have the Same Inventors.

All of the evidence of record supports one conclusion: the Bookbinder reference and the Pending Claims share the same inventors.

During the prosecution of the ’171 Application, the PTO issued a restriction requirement. (PFoF ¶ 15.) In response, and after electing the Pending Claims to be pursued for prosecution, Halozyme petitioned the PTO to correct the inventorship and remove individuals who contributed only to the withdrawn claims. (PFoF ¶ 16.) Those petitions identified Louis Bookbinder, Anirban Kundu, and Gregory Frost as the joint inventors on the ’171 Application. (PFoF ¶ 16.) The PTO formally corrected inventorship on the ’171 Application identifying Louis Bookbinder, Anirban Kundu and Gregory Frost as the joint inventors. (PFoF ¶ 17.)

WO 2004/078140 (Bookbinder), which had been published on September 16, 2004, also lists Louis Bookbinder, Anirban Kundu and, Gregory Frost as the joint inventors. (PFoF ¶ 18.) Therefore, Bookbinder published less than one year prior to the ’171 Application’s claimed priority date of the ’716 Application, which was filed on February 23, 2005. (PFoF ¶ 18.) Accordingly, the inventors on Bookbinder and the ’171 Application are the same. (PFoF ¶ 19.)

C. Section 102(a)/(e)’s “By Another” Does Not Require “Inventive Contribution to the Conception” of the Claimed Invention.

The evidence set forth above is sufficient and Halozyme need not establish more to show that Bookbinder and the Pending Claims have the same inventors. This is true for at least two reasons.

First, inventorship of the ’171 Application is not at issue in this case. Neither the Examiner nor the PTAB rejected the Pending Claims on inventorship grounds, and the PTO

never raised inventorship as it relates to conception, Section 102(a) or Section 102(e) as grounds for rejecting the '171 Application. It is legally improper to do so now. Halozyme brought this action pursuant to 35 U.S.C. § 145 to seek a judgment that it is entitled to a patent, i.e., the PTAB's rejections (none of which were based on incorrect inventorship) are wrong. Specifically, Halozyme objected to the final decision of the PTAB affirming the Examiner's obviousness rejections under 35 U.S.C. § 103(a) and non-statutory obviousness-type double patenting. These grounds form the proper scope of this Section 145 action.

The Federal Circuit stated, and the Supreme Court later affirmed, that a Section 145 action is "not an entirely de novo proceeding" in that "[i]ssues that were not considered by the Patent Office cannot be raised with the district court in most circumstances, and if no new evidence is introduced, the court reviews the action on the administrative record, subject to the court/agency standard of review." *Hyatt v. Kappos*, 625 F.3d 1320, 1322 (Fed. Cir. 2010), *aff'd*, 132 S. Ct. 1690 (2012). The Federal Circuit continued: "The particular significance of a § 145 civil action is that it affords an applicant the opportunity to introduce new evidence after the close of the administrative proceedings—and once an applicant introduces new evidence on an issue, the district court reviews that issue de novo. Thus, an applicant's ability to introduce new evidence is the hallmark of a § 145 action." *Id.* (emphasis added). Section 145 does not permit the PTO to raise new issues of patentability.

Second, proving inventorship through conception is a distinct ground of patentability that is not required in determining whether the Bookbinder reference is prior art under 35 U.S.C. § 102(a) or 102(e). Section 102(a) states:

> A person shall be entitled to a patent unless . . . the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent

35 U.S.C. § 102(a). Section 102(e) states:

> A person shall be entitled to a patent unless . . . the invention was described in—(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for the purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language

35 U.S.C. § 102(e). It is well-settled that one's own invention, whatever form of disclosure to the public, may not be prior art against oneself, absent a statutory time bar. *In re Katz,* 687 F.2d 450, 454 (Fed. Cir. 1982).

The PTO's own Manual of Patent Examining Procedure ("MPEP") states that "by another" means "other than applicants . . . in other words, a different inventive entity. The inventive entity is different if not all inventors are the same." MPEP § 2136.04 (citing *In re Land,* 368 F.2d 866 (CCPA 1966)). Neither Sections 102(a) nor102(e) nor the MPEP require for patentability, proving inventorship or conception, in contrast to other statutory provisions that do. *See, e.g.*, 35 U.S.C. § 102(g).

II. The Pending Claims Are Not Obvious Under 35 U.S.C. § 103 over Claims 9 and 10 of the '429 Patent in View of Braxton and Thompson.

A. Properly Construed, the Terms of Claim 264 Require a Pharmaceutical Composition Formulated for Systemic Administration.

Turning first to claim construction, there are several material claim term differences between the Pending Claims and Claims 9 and 10 of the '429 Patent. Claim 264 of the '171

Application, upon which Pending Claims 295-298, 300 and 303 depend,[3] contrasts to Claim 10 of the '429 Patent[4] as follows:

Pending Claim 264, '171 Application	**Claim 10, '429 Patent**
264. A *pharmaceutical composition,* comprising a PEGylated hyaluronidase in a *pharmaceutically acceptable carrier,* wherein:	
	10. The hyaluronidase glycoprotein of claim 9, wherein the polymer is PEG or dextran. 9. The hyaluronidase glycoprotein of claim 7, wherein the hyaluronidase glycoprotein is modified with a polymer.
the hyaluronidase contains about three to six PEG moieties per hyaluronidase molecule	

[3] Halozyme narrowed the appealed claims to Claims 295–298, 300 and 303. These claims, however, depend on Claim 264, which means the limitations of Claim 264 are incorporated into the Pending Claims.

[4] Claim 10 of the '429 Patent is dependent on Claim 9, which is dependent on Claim 7 of the '429 Patent. Accordingly, all three claims are considered in an analysis of obviousness-type double patenting of Claim 10.

Pending Claim 264, '171 Application	**Claim 10, '429 Patent**
the hyaluronidase polypeptide is a human- derived hyaluronidase	7. A substantially purified hyaluronidase glycoprotein, wherein the hyaluronidase glycoprotein: is soluble; is neutral active; contains at least one sugar moiety that is covalently attached to an asparagine (N) residue of the polypeptide; and consists of the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 set forth in SEQ ID NO:1 or contains amino acid substitutions in the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1, whereby the amino-acid substituted hyaluronidase glycoprotein consists of a sequence of amino acids that has at least 95% amino acid sequence identity with the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1.
and ***the composition is formulated for*** *systemic administration*	

(PFoF ¶¶ 24, 34–37 (emphasis added).)

Claim 264 plainly requires a pharmaceutical composition containing a specifically "formulated" human derived hyaluronidase of three to six PEGs for systemic administration. Properly construed as read by one of ordinary skill, those limitations in combination convey to one of ordinary skill in the art that there must be a suitable serum half-life and activity for the pharmaceutical composition to be used for systemic administration. (PFoF ¶ 25.)

In ODP claim construction, the actual language of the claims as understood by one of skill is paramount, but the specification may be consulted for the limited purpose of construing

limitations found in the claims. *Eli Lilly*, 689 F.3d at 1380. There are several reasons why Halozyme's claim construction is the better one in this case.

First, read as a whole by one of skill, the claim 264 language reveals that the preamble's phrase "pharmaceutical composition" is carried into the body of the claim by the claim limitation that "the composition is formulated for systemic administration." This plainly refers to the antecedent "pharmaceutical composition" in the preamble. Therefore, the "pharmaceutical composition" is not just preamble language that is not limiting. It is in the body of the claim and therefore is limiting.

Second, the '171 Application's specification teaches that the specifically formulated human hyaluronidase with about three to six PEG moieties, as a pharmaceutical composition for use in systemic administration, has a serum "half-life" and "activity," as plainly disclosed in the specification's example 21A. (PFoF ¶ 32.) This example in the specification supports Halozyme's construction. Reading the claim otherwise is explicitly contrary to the specification's example that shows activity and serum half-life.

Third, the teachings of the specification as read by one of ordinary skill in the art are that one of skill would understand that the Claim 264's limitations of "pharmaceutical composition" and formulated for "systemic administration," along with the intended utility, all illustrate that level of serum half-life and therapeutic effect at the distal tissues are limitations of the inventions claimed. (PFoF ¶ 33.)

Fourth, the Claim 264 terms "pharmaceutical composition," "the hyaluronidase contains about three to six PEG moieties per hyaluronidase molecule," and "the composition is formulated for systemic administration" are not present in the '429 Patent claims. Thus, any attempt to attach or read in those limitations in the proper construction of Claims 9 and 10 of the

'429 Patent would be error. The PTO recognizes this basic principle in MPEP 804.II.B.2.(a): "Subject matter disclosed in the reference patent [(here the '429 Patent)] or application that does not fall within the scope of a reference claim cannot be used to construe the claim in the context of a nonstatutory double patenting analysis as this would effectively be treating the disclosure as prior art."

B. The '171 Application Claim 264 and the '429 Patent Claims 9 and 10 Are Patentably Distinct.

The difference between the claims is apparent.

- Claim 264 claims a pharmaceutical composition that is formulated for systemic administration that includes a specific human derived hyaluronidase containing about three to six PEG moieties per hyaluronidase molecule.[5]
- By contrast, Claim 10 of the '429 Patent claims a compound of human-derived hyaluronidase that is modified by a polymer, including any PEG or any dextran molecule, without limitation as to number, or whether such modification is suitable for a pharmaceutical composition to be used for systemic administration.

These differences render the claims patentability distinct, particularly when assessed as a whole in the context of all claim elements. *See Eli Lilly*, 689 F.3d 1368 at 1377 ("so too must the subject matter of the [] claims be considered 'as a whole' to determine whether the [] Compound would have made those claims obvious for purposes of obviousness-type double patenting.")

[5] Claims 295-298, 300 and 303 further claim specific amino acid sequences of the human derived hyaluronidase—a further point of distinction when the claims are read as a whole. Read as a whole, the Pending Claims recite a specific species of human-hyaluronidase with about three to six PEG moieties that is a pharmaceutical composition formulated for systemic administration.

1. The State of the Art Shows That There Was Great Uncertainty To Motivate and Have a Reasonable Expectation of Success To Achieve a Pharmaceutical Composition of Three to Six PEGs to the Specific Human Hyaluronidase for Systemic Use.

Halozyme's experts show that the general state of the art on PEGylating for achieving the balance of sufficient enzymatic activity and prolonged circulation for enzymes that act on macromolecular substrates (such as hyaluronidase) was, and continues to remain very challenging with a low expectation of success, particularly by nonspecific amine-directed PEGylation. (PFoF ¶ 20.) Compounding the issue, as Halozyme's experts show, this specific protein, human-derived hyaluronidase, is a virtually unique glycoprotein that presents specific issues on whether one of skill would be motivated to PEGylate it with three to six PEG moieties to be used in a systemic administration where activity must be achieved at distal tissues, much less have a reasonable expectation of success. (PFoF ¶ 21.) It was no simple matter to successfully make this human derived hyaluronidase with about three to six PEG moieties for use in a systemic application that would have suitable activity and half-life in the body to reach the distal tissues, as the inventor also testified. (PFoF ¶ 23.)

2. The Evidence Shows that the Braxton and Thompson References Do Not Supply the Range, Motivation, or Reasonable Expectation of Success.

As Halozyme's experts explained, the PTAB's reliance on Braxton and Thompson to supply (i) the 3-6 PEG claim elements, (ii) motivation to combine, and (iii) reasonable expectation of success was misplaced. (PFoF ¶¶ 47–51.)

At its core, the PTAB erred by failing to appreciate that one of ordinary skill would understand that Braxton and Thompson teach PEG conjugations to cysteine amino acids that if

done with human-derived hyaluronidase, would likely destroy the requisite activity of the human-derived hyaluronidase, rendering it inoperable. (PFoF ¶ 53.)[6]

Braxton itself states that the then-standard lysine approach "suffers from the problems associated with partial, random modification of protein and the potential for losing activity if lysine residues are essential for biological activity." (PFoF ¶ 48.) Halozyme's experts testified that a person of ordinary skill in the art would have read Braxton and Thompson as discouraging one of ordinary skill in the art from being motivated to use non-specific PEGylation at the lysine residues for proteins intended for therapeutic use as pharmaceutical compositions, much less having a reasonable expectation of success. (PFoF ¶¶ 49–51); *Millennium Pharmaceuticals, Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1366 (Fed. Cir. 2017) ("A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant.").[7] Moreover, as Halozyme's experts opined, one of skill reading Braxton would understand that its specific range of PEG moieties provides no more than a generalized teaching that is inapplicable to this specific protein. (PFoF ¶ 50.)

Finally, Dr. Flamion explained cogently the error of the PTAB's conclusion that the Pending Claims employ routine optimization. The PTAB's decision says nothing more than what was generalized in the art, namely attach one or more PEGs to a protein without abolishing its

[6] Further, Braxton and Thompson's preference for mono-PEGylation at the cysteine residues teaches away from the about three to six PEG moieties as required in Claim 264. (PFoF ¶ 54.) Finally, Thompson teaches making a "dumbbell" conjugate of a R1-PEG-R2 structure where PEG serves as a spacer in these "dumbbell" constructs, not a properties modifier, like in the claimed invention of the '171 Application. (PFoF ¶ 52.)

[7] Dr. Zalipsky also opined that site-specific PEGylation, not lysine PEGylation, would have been a more favored approach for the claimed invention of the '171 Application. (PFoF ¶ 57.)

activity. (PFoF ¶ 21.) At best, this is a general plan or hypothesis and it does not teach one of skill the general or specific conditions required for any particular number of PEGs (much less where) to attach to the claimed composition which has approximately 447 amino acids without abolishing its in vivo activity, much less on a glycosylated protein where the glycans are essential for activity in a manner that does not interfere with the in vivo activity at the distal tissues. (PFoF ¶ 21.) The claimed human-derived hyaluronidase has 30 lysines and an N-terminal amino group that result in a large number of potential PEGylation sites. (PFoF ¶ 21.) Moreover, neither Thompson nor Braxton provide the solution or the general or specific conditions applicable to this unique protein in order to achieve the invention claimed. (PFoF ¶ 21.)

In sum, the PTAB never received this evidence on Braxton and Thompson, and that evidence, had the PTAB received it, shows the PTAB fundamentally erred in using Braxton and Thompson to provide the missing but required obvious analysis elements at least of (a) supplying the missing range of PEG-moieties, (b) providing a motivation to combine the references, and (c) providing a reasonable expectation of success. *See In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1069 (Fed. Cir. 2012) (a party seeking to invalidate a patent as obvious must demonstrate "that a skilled artisan would have reason to combine the teaching of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success from doing so.").

III. The PTAB's Obviousness Type Double Patenting Rejections of the Pending Claims Based on Claims 4 and 5 of the '431 Patent in View of Braxton and Thompson Were Error.

There are several reasons why the PTAB erred in finding the Pending Claims obvious over Claims 4 and 5 of the '431 Patent in view of Braxton and Thompson.

First, Dr. Zalipsky opined that one of ordinary skill in the art would not have used the teachings of Braxton and Thompson to make the claimed PEGylated human-derived

hyaluronidase with about three to six PEG moieties for the same reasons discussed above. For example, Braxton and Thompson's preference for mono-PEGylation at the cysteine residues teach away from the about three to six PEG moieties as required in Claim 264. (PFoF ¶ 54.) Additionally, both Braxton and Thompson teach away from using the random, multi-PEGylation of lysine residues stating that such approach often leads to loss of activity and high composition heterogeneity making the conjugates unsuitable for pharmaceutical compositions. (PFoF ¶ 55.) Finally, one of ordinary skill would not know whether 3-6 PEGs would retain sufficient activity and circulatory serum half-life to make it suitable for use as a pharmaceutical composition formulated for systemic administration as claimed in the '171 Application because the claimed human-derived hyaluronidase contains many residues that could potentially be PEGylated, and there are many additional variables that may lead to an uncertain outcome. (PFoF ¶ 56.)

Second, Claim 264's additional requirement that the "pharmaceutical composition" is "formulated for systemic administration" renders it patentably distinct from Claim 5 of the '431 Patent. (*See supra* Part II.) Thus, the Pending Claims are also patentably distinct from Claim 5 of the '431 Patent for the same reasons and further in view of the specifically claimed amino acid sequences. (*See supra* note 5.)

Third, the use of term "comprising" in the patent does not include additional therapeutic components, such as the insulin used in the '431 Patent. Although it is true that the word "'comprising' . . . creates a presumption that the body of the claim is open," *Crystal Semiconductor Corp. v. TriTech Microelecs. Int'l, Inc.*, 246 F.3d 1336, 1350 (Fed. Cir. 2001), it "is not a weasel word with which to abrogate claim limitations," *Dippin' Dots, Inc. v. Mosey*, 476 F.3d 1337, 1343 (Fed. Cir. 2007). "The presumption raised by the term 'comprising' does not

reach into [a claim] to render every word and phrase therein open-ended . . . ." *Id.* The claim must still be interpreted consistently with the specification. *Id.* at 1342–1343 (affirming the district court's limitation of the scope of a claim based on the patent's written description, despite the use of the word "comprising" in the claim). The '171 Application Pending Claims do not claim a pharmaceutical composition comprising a PEGylated human derived hyaluronidase with about three to six PEGs formulated for systemic administration and insulin. Thus, the use of the term "comprising" in Claim 264 does not broaden the scope of the claim to include additional therapeutic components.

This important subject matter distinction renders any reliance the '431 Patent's specification faulty. The '431 Patent's specification does not disclose the separate and distinct composition claimed in Claim 5 of the '431 Patent—a combination of human derived hyaluronidase and insulin. *See Eli Lilly*, 689 F.3d at 1380 (reference disclosure may be viewed only for claim construction or utility of a disclosed compound to assess whether subsequent pending claim to method of using that compound is described in the reference patent).

IV. The PTAB's Obviousness Type Double Patenting Rejections of the Pending Claims Based on Claims 5 and 6 of the '081 Patent in View of Braxton and Thompson Were Error.

The analysis for this branch of the PTAB's decision follows from the previous section, except that Claim 5 of the '431 Patent includes "insulin" and Claim 6 of the '081 Patent uses "cosmetic agent." Accordingly, and as Dr. Flamion testified, the Pending Claims are patently distinct from Claim 6 of the '081 Patent. (PFoF ¶ 46; *see also supra* Parts II–III.)

V. Secondary Considerations Also Support the Conclusion That the Pending Claims Are Not Obvious.

Halozyme buttressed its nonobviousness position with evidence establishing one or more the secondary considerations of nonobviousness. Those secondary considerations are

"'commercial success, long felt but unsolved needs, failure of others,' and unexpected results." *Novartis AG v. Noven Pharms. Inc.*, 853 F.3d 1289, 1292 (Fed. Cir. 2017) (quoting *Graham*, 383 U.S. at 17). As discussed below, all of these considerations are supported by the record.

A. Commercial Success.

The specific pharmaceutical composition product embodying the '171 Application (known as PEGPH20) has been commercially successful. It is true that there have been no sales of PEGPH20, but the doctrine of commercial success is not limited to products that can be sold. *Cf. NantKwest, Inc. v. Lee*, 2015-2095, 2017 WL 1735330, at *8 (Fed. Cir. May 3, 2017) (rejecting commercial-success claim in a preapproved-product case because the applicant did not establish a nexus between the evidence of success (investments) and the claimed invention and not because investments could never establish commercial success).

In this case, there is sufficient objective evidence of economic activity taken because of the features of PEGPH20 that Halozyme seeks to patent. First, Halozyme has raised significant sums of funds ($135 million) from investors because of PEGPH20. (PFoF ¶ 58.) Unlike in *NantKwest*, Halozyme has evidence connecting the investment to PEGPH20. The company's presolicitation filings with the SEC state that the purpose of the funds sought is to develop the PEGPH20 product. (PFoF ¶ 59.) In fact, the PEGPH20 product is the only specific purpose of the fundraising effort. The presentation made by Halozyme to potential investors is consistent. The first reason given by the company to invest in it—and the one to which most of the presentation's space is devoted—is the PEGPH20 product. (PFoF ¶ 60.) The Court can reasonably infer from this evidence that investors chose to invest in Halozyme because of the PEGPH20 product.[8]

[8] The PEGPH20 product incorporates the Pending Claims. (PFoF ¶ 62.)

Second, other entities have entered clinical-study and other partnerships with Halozyme because of the PEGPH20 product. Halozyme has agreements with a nationally recognized cancer center, a public university, and a hospital system regarding clinical study of the PEGPH20 product and has been approached by at least two other universities. (PFoF ¶ 61.) Most of these research partners sought Halozyme out and not the other way around. (PFoF ¶ 61.) In addition, Halozyme has an agreement with a large pharmaceutical company in which each company will study the other's product. (PFoF ¶ 61.) Finally, Halozyme has an agreement with a national organization focused on pancreatic cancer that will facilitate the clinical study of the PEGPH20 product. (PFoF ¶ 61.) Regardless of the status of them, or the fact that Halozyme derives no revenue from them, these arrangements demonstrate that others are seeking Halozyme out because of the PEGPH20 product.

B. Other Secondary Considerations.

In addition to commercial success, the other secondary considerations support the conclusion that the pending claims are not obvious.

1. Unexpected Results.

As explained previously, one of ordinary skill armed with the knowledge that the half-life of human hyaluronidase is extremely short and PEGylation generally causes a decrease in protein activity would not have expected useful therapeutic results as required by the Pending Claims from modifying rHuPH20 with PEGylation, much less with 3-6 PEG moieties. (PFoF ¶ 63.) The claimed PEGylated rHuPH20 of the '171 Application overcomes problems associated with systemic administration of native rHuPH20 as claimed in '140 Bookbinder, namely short half-life and insufficient enzymatic activity. (PFoF ¶ 63.) Importantly, it is the addition of 3-6 PEG moieties that retains the necessary properties (i.e., increase half-life while retaining sufficient enzymatic activity) to make it useful as a therapeutic or pharmaceutical

composition for systemic (intravenous) administration as claimed in the '171 Application. (PFoF ¶ 63.)

In addition, the molecular weight of each individual PEG moiety and the total molecular weight of the end product conjugate have a great impact on the activity of enzymes with large macromolecular substrates. (PFoF ¶ 64.) For such enzymes, smaller molecular weight PEGs are generally preferred to preserve enzyme activity. (PFoF ¶ 64.) Additionally, mono-PEGylation is particularly preferred via site-specific modification to minimize activity impairment. rHuPH20 is already a large enzyme in its native form that catalyzes a macromolecular substrate, hyaluronan. (PFoF ¶ 64.) One of ordinary skill would expect that in such case, smaller molecular weight PEG moieties and fewer PEGs, with a preference to mono-PEGylation would be required to balance the need to increase half-life while retaining sufficient enzymatic activity for use as a therapeutic. (PFoF ¶ 64.) The inventors' data showing that the attachment of up to 3-5 PEG moieties, each of molecular weight 30 kDa, was required to achieve maximum increase in half-life while still retaining substantial enzymatic activity is a surprising and unexpected result. (PFoF ¶ 64.) This is an unusually high number to retain such enzymatic activity considering the large molecular weight of the enzyme and substrate. (PFoF ¶ 64.) None of the cited references, singly or in combination, teach or suggest that 3-6 PEG moieties as claimed in the PEGylated rHuPH20 of the '171 Application is important and necessary to achieve the balance of significantly increasing half-life while retaining sufficient enzymatic activity for use as a therapeutic. (PFoF ¶ 64.)

2. Long-Felt-but-Unmet Need.

PEGPH20 meets a medical need that is not being met by currently available therapeutics in this area.

As discussed above, the differences in the prior art were complex and the challenges faced by the Halozyme inventors stemmed from a multitude of different available approaches

and unpredictable results of attempting to apply such approaches to meet such needs. (PFoF ¶ 65.) PEGPH20 meets a long-felt medical need that is not met by currently available medications. (PFoF ¶ 65.) Currently, it is the only product of its kind, comprising a unique therapeutic in comparison to existing therapies in that PEGPH20 has been shown to achieve significant improvements in intratumoral perfusion and drug delivery through targeting of co-administered cancer therapies, especially for pancreatic cancer (as discussed further below), which is one of the deadliest cancers around. (PFoF ¶ 65.) PEGPH20 has little toxicity of its own since it does not attack the DNA or other essential molecular machinery within cells, as chemotherapeutic agents do. (PFoF ¶ 65.) This allows PEGPH20 to be combined with these chemotherapies without increasing their toxicities in a significant way. (PFoF ¶ 65.)

The mechanism of action of Halozyme's PEGPH20 in various types of cancer is to target and deplete hyaluronan in the tumor microenvironment and thereby increase access for therapeutics. (PFoF ¶ 66.) Halozyme has focused on "[t]umors with High Unmet Need" including first-line metastatic pancreatic cancer and advanced non-small cell lung, second-line metastatic gastric, and second-line stage IV breast cancers. (PFoF ¶ 66.) One example is pancreatic ductal adenocarcinoma (PDAC). PDAC has "claimed notoriety by proving to be one of the most recalcitrant solid-organ malignancies. As a telltale sign of its lethality, PDAC accounts for less than 3% of new cancers diagnosed annually in developed nations and in the United States, yet it is the fourth leading cause of cancer related mortality. Ominously, PDAC is also poised to surpass breast, prostate and colon cancers to become the second leading cancer related cause of death by 2030." (PFoF ¶ 66.) Notably, most patients with PDAC are not candidates for surgical resection owing to the late stage at presentation, and even those patients with early-stage disease who undergo surgical resection and adjuvant therapy eventually relapse

and succumb to it. (PFoF ¶ 66.) In exploring recent advances in molecularly targeted therapies in PDAC, Narayanan and Weekes stated that "PEGPH20 [co-administered with] gemcitabine resulted in an 83% increase in survival and a dramatic decrease in metastatic burden in mice, owing to the enhanced delivery of gemcitabine to the tumor." (PFoF ¶ 66.) The authors go on to note that initial phase II trial reports "demonstrate that patients with high hyaluronan expressing tumors have greater clinical benefit." (PFoF ¶ 66.)

3. Industry Praise and Recognition.

PEGPH20 has raised considerable recognition and praise in the scientific and medical communities. PEGPH20 is not yet approved by the FDA, but is currently undergoing clinical trials with positive and promising results. (PFoF ¶ 67.)

Further, these promising results have garnered strong interests by others in the field to investigate the potential of this novel class of anticancer therapy as shown by Halozyme's engagement in many partnerships and clinical collaborations to advance PEGPH20. For example, Halozyme and a major pharmaceutical company entered into a Combination Study Agreement in November 2016 to use PEGPH20 in combination with cisplatin and gemcitabine and/or atezolizaumab in subjects with previously untreatable gallbladder cancers in a clinical study. (PFoF ¶ 68.) In another example, a national organization focused on pancreatic cancer entered into an agreement with Halozyme in December 2016 to use Halozyme's PEGPH20 in subjects diagnosed with pancreatic cancer. (PFoF ¶ 68.)

Halozyme also receives numerous applications from third parties for investigator sponsored trials. (PFoF ¶ 69.) These types of applications have resulted in a number of Investigator-Initiated Clinical Research Study Agreements between Halozyme and third party entities. (PFoF ¶ 69.) These clinical collaborations and Investigator-Initiated Clinical Research

Study Agreements are a direct result of the industry's recognition of and desire for the claimed invention of the '171 Application. (PFoF ¶ 69.)

CONCLUSION

Halozyme believes the evidence at trial will support its proposed findings and that the law supports its proposed conclusions. Accordingly, Halozyme urges the Court to—following the trial—make the above findings and conclusions and enter judgment in Halozyme's favor.

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Respectfully submitted,

/s/

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CERTIFICATE OF SERVICE

I hereby certify that on November 13, 2017, I electronically filed the foregoing **Halozyme's Pretrial Proposed Findings of Fact and Conclusions of Law** with the Clerk of Court using the ECF system, which will send notification of such filing to all ECF participants.

/s/

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